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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/641,471	08/18/2000	Carol M. Kinoshita	10278-017001	6615

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EXAMINER
SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	19

DATE MAILED: 09/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/641,471	KINOSHITA ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81-106 and 109-185* is/are pending in the application.

4a) Of the above claim(s) *81-104 and 172-183* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *105,106,109-171, 184 and 185* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed July 16, 2003 amending the specification to correct clerical errors, amending claims 105, 125, 126, 139-142, 147, 156, 157 and 166, canceling claims 107, 108, 132, 143 and 165 and adding claims 172 and 173 has been entered.

Prior to the above amendment, the last claim in the instant application was claim 183. In accordance with 37 CFR § 1.126, the newly added claims have been renumbered 184-185. The new numbers have been used thenceforth.

Claims 81-106 and 109-185 are pending. Claims 81-104 and 172-183 are withdrawn.

Claims 105, 106, 109-171, 184 and 185 are under consideration.

Specification

The use of the trademark has been noted in this application on pages 23; 24; 41-45; page 51, line 16, for example. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

While the specification has been amended, the trademarks are not capitalized.

The disclosure is objected to because of the following:

On page 51, line 16, the specification has been amended to insert "activated endogenous glucocerebrosidase" before "Gene-Activated ™ GCB". An enzyme can be activated in many ways. Therefore, said "spelling out" is not adequate representation of the term "Gene-Activated ™ GCB". Applicants should indicate the source from which HT-1080 cells producing GA-GCB were obtained and which sequence is used for activation of an endogenous GCB gene.

Appropriate correction is required.

Claim Objections

Claim 166 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 166 depends from claim 139 which is drawn to a method of use of a human cell. Claim 166 recites the limitation "wherein the cell is a human cell".

Claim 184 is objected to because of the following informalities:

It is suggested that applicants maintain consistency through out the claims and insert the abbreviation "(CHO)" after "Chinese hamster ovary".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 144-147 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 144-146 are incomplete as dependent from canceled claim 143.

Claim 147 is incomplete as dependent from canceled claim 1.

For the purposes of compact prosecution, claim 144-146 are construed as dependent from claim 139 and claim 147 as dependent from claim 144.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 105, 106, 109-171, 184 and 185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. in view of Smith et al.

Friedman et al. (US Patent 5,549,892, form PTO-1449 filed November 30, 2000, reference AD) teach the importance of a glycoprotein, human GCB, needed for treatment of Gaucher's disease. They teach the importance of GCB remodeling for the production of a pharmaceutically effective preparation and the production of a remodeled recombinant human GCB in CHO cells. The sequence encoding human GCB comprises exogenous regulatory and coding sequences (columns 3-4). Friedman et al. teach that the remodeling of the carbohydrate chains may be accomplished by several different alternative ways such as utilizing mutant cell lines deficient in certain carbohydrate synthetic pathways (column 6, lines 1-15).

Smith et al. (US Patent 5,939,279) teach the method of preparing high mannose $Man_9(GlcAc)_2$ glycoproteins by treating human HT-29 cells with mannosidase I inhibitors, deoxymannojirimycin or kifunensine (columns 7-8, column 9, claim 8). With regard to claims 109 and 110, Smith et al. teach the required range of the kifunensine concentration (column 8, lines 24 and 25). With regard to claims 111-114, Smith et al. teach the required range of the swainsonine concentration (column 8, line 26). One of the glycoproteins present in HT-29 cells is GCB.

Therefore, at the time the invention was made, the importance of remodeling GCB to produce hmGCB has been known. The mannosidase inhibitors as tools to prepare human hmGCB have been known. The genetic manipulation of protein

expression and techniques to make a knockout gene of a known structure and antisense molecule therefor were known.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare hmGCB obtained from HT-29 or other mammalian cells using method of Smith et al. One of ordinary skill in the art at the time the invention was made would have been motivated to specifically purify GCB in view of its importance taught by Friedman et al. The high expectation of success is provided by Smith et al. who teach the requisite step for preparing remodeled glycoproteins while the purification of proteins from the cells is standard in the art and is taught by Friedman et al., for example.

With regard to claims 127, 128, 139-171, 184 and 185 it would have been obvious to use a known mammalian/human cell line in view of its availability. It would have been obvious to increase the production of GCB in the cells by the introduction of additional copies of a GCB gene and/or by introducing the exogenous regulatory sequence that would increase the expression of an endogenous GCB. Such techniques are standard in the art and are widely used for the increased production of the proteins of interest.

Response to Arguments

Applicant's arguments filed July 16, 2003 have been fully considered but they are not persuasive.

With regard to the 103(a) rejection Applicants argue that "the prior art must provide a motivation and reasonable expectation of success to arrive at the specifically claimed methods. Such motivation is nowhere to be found in the cited references. The Examiner has provided no evidence of a specific motivation to contact a cell expressing GCB with the specifically recited molecule, kifunensine" (Remarks, page 17). The examiner disagrees with that. In fact, Smith does exactly this, i.e. teaches *to contact a HT-29 cell expressing GCB with the specifically recited molecule, kifunensine*, producing a cell comprising high mannose proteins including GCB (columns 8-9, Example 8, Table II). The difference between the teachings of Smith and claim 105, for example, is that the GCB activity was not measured in these cells. Friedman et al. provide motivation to isolate GCB from said cells in view of therapeutic importance of GCB. Alternatively, Friedman et al. teach the importance of the carbohydrate remodeling of GCB for its effective targeting to phagocytes in preference to non-phagocytic cells in patients with Gaucher's disease (columns 1-2). Therefore, there is a motivation to obtain a hmGCB by known means. Kifunensine is one of such well known means used in remodeling.

Applicants further argue that "the claimed methods have surprisingly advantageous properties. As discussed at page 53, lines 17-21, uptake of GCB from kifunensine treated cells was 14-fold over background and 73% inhibitable by mannan. Uptake of GA-GCB from untreated cells was approximately 3-fold over background and 53% inhibitable by mannan. Thus, the claimed methods provide GCB having surprisingly advantageous properties" (page 19). This is not found persuasive in view of the following considerations. First, the comparison with the background, i.e. buffer with no GCB, is not relevant to the evaluation of unexpected results. What is relevant is the difference between GCB from cells treated with kifunensine and GCB from untreated cells. In the instant invention, uptake of GCB from kifunensine treated cells was about 4-fold higher than the uptake of GCB from untreated cells (page 54, Table 2). The art teaches that it is highly reasonable to expect the increase in hmGCB in kifunensine treated cells (e.g., Smith, *supra)*. Applicants do not provide evidence as to why the observed 4-fold increase is unexpected. To evaluate whether the increase observed in the instant case is unexpected, it is reasonable to compare the magnitude of said increase with an increase achieved by GCB remodeling in mammalian cells using means other than kifunensine. The art teaches that it is reasonable to expect up to about 5-fold increase in the uptake using remodeled GCB such as the glycosidase-treated GCB, for example (Furbish et al., BBA (1981) 673, 425-434, specifically page 429, Table I, form PTO-1449 filed February 8, 2002, reference AL). Thus, it appears

that the 4-fold increase obtained in the instant invention can not be considered as an unexpected result.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Elbein et al. (JBC (1990) 265, 15599-15605, form PTO-1449, filed November 30, 2000, reference AN) teach that kifunensine is a highly potent mannosidase I inhibitor, much more effective than deoxymannojirimycin (paragraph bridging pages 15600-15601).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

September 11, 2003